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Zonisamide for the treatment of myoclonic seizures in progressive myoclonic epilepsy: an open-label study

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ABSTRACT – *Purpose.* To examine the safety and efficacy of zonisamide in treating myoclonic seizures associated with progressive myoclonic epilepsy (PME), in an open-label setting. *Methods.* Thirty patients with refractory PME (aged ≥ 5 years), who were taking up to three antiepileptic drugs, received adjunctive zonisamide (≤ 6 mg/kg/day) therapy for 16 weeks. Myoclonic seizures were recorded daily over a 24-hour period or in 10-minute epochs in the morning, afternoon, and evening. Safety was assessed via adverse events (AEs); efficacy was measured by the percentage of patients experiencing a ≥ 50% decrease in myoclonic seizure frequency from baseline. *Results.* Treatment-related AEs, experienced by 53% (n = 16/30) of patients, led to five patients discontinuing zonisamide. The most common AEs were decreased appetite, somnolence, and asthenia. Overall, 36% of patients (n = 10/28) had a ≥ 50% reduction in myoclonic seizure frequency. *Conclusions.* These results suggest that zonisamide may be useful in the treatment of patients with PME. However, due to the size and open-label character of this study, further research is required.

Key words: zonisamide, progressive myoclonic epilepsy, antiepileptic drug, myoclonic seizures

Progressive myoclonic epilepsy (PME) is a clinical syndrome with multiple etiologies characterized by myoclonic seizures and neurodegeneration (Conry, 2002). Seizure types other than myoclonic seizures are almost always present, and ataxia and dementia are the most frequent neurological findings. In addition, seizures are often refractory to medication (Leppik, 2003). However, very few antiepileptic drugs (AEDs) are commonly used for the treatment of myoclonic seizures in PME; valproate being the drug of choice. Off-label use of newer drugs, such as levetiracetam (Kinrions *et al.* 2003, Mancuso *et al.* 2006) and zonisamide (Henry *et al.* 1988; Kyllerman and Ben-Menachem, 1998), has suggested potential efficacy against myo-

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clonic seizures in PME. In 1988, Henry *et al.* treated two PME patients with zonisamide. After therapy was initiated, both patients experienced a marked decrease in seizure frequency and significant improvement in quality of life. Similarly, in 1998, Kyllerman and Ben-Menachem treated seven patients with PME. These patients had experienced intractable seizures in spite of standard anticonvulsant regimens, usually valproate and benzodiazepine. After zonisamide therapy was initiated, they found that the numbers of both myoclonic and tonic-clonic seizures were dramatically reduced. Currently, zonisamide is licensed in the United States (US) and Europe for adjunctive treatment of partial seizures in adults, and in Japan for a range of epilepsy syndromes, including PME, in adults and children. The objective of this open-label US study was to evaluate the safety and potential efficacy of zonisamide in treating a larger number of patients with PME.

Methods

This phase IV, open-label, multicenter study (ZNS-502) investigated zonisamide as add-on therapy in patients with refractory PME, focusing on myoclonic seizures. Inclusion criteria were: male and female patients (≥ 5 years) with a primary diagnosis of PME (as defined by the International Classification of Epilepsies and Epileptic Syndromes – *Appendix 1*), stable use of up to three other concomitant AEDs, and written, informed consent. After a 2-week baseline, zonisamide was initiated at 0.4 mg/kg/day and titrated up for efficacy and tolerability (based on the investigator's judgment) or to a maximum of 6 mg/kg/day over eight weeks. Patients then entered an 8-week maintenance period and continued on this zonisamide dosage. Change in concomitant medication was permitted if clinically necessary.

Safety was assessed via adverse events (AEs), classified by the investigator for severity and relationship to zonisamide. AEs were coded using COSTART terminology.

Efficacy was assessed by the proportions of patients reporting ≥ 50% and ≥ 75% reductions in myoclonic seizures in the intent-to-treat population, and by the median percentage reduction in myoclonic seizure frequency from baseline to the end of the maintenance phase (week 16) in the overall study population. Patients/caregivers counted and recorded seizures, either over 24-hour periods or during 10-minute epochs in the morning, afternoon, and evening, at the same times each day. In general, 10-minute counts were used in patients with high seizure frequency. When the latter counting method was used, an average 10-minute count across these three time points was calculated. The 24-hour counts were converted to 10-minute counts and combined with the average of the three 10-minute counts to create a converted 10-minute count, permitting overall analysis of the study population. The separate categories of seizures counted were myoclonic, typical absence, atypical absence, tonic, clonic, atonic, and tonic-clonic, but only myoclonic seizures were assessed as part of this study. A myoclonic seizure was defined as a sudden, brief, muscular jerk involving the limbs, neck or trunk (singly or in some combination), occurring as a single or irregularly recurrent event according to the International League Against Epilepsy (Engel, 2006).

Table 1. Patient demographics and concomitant AED use.

	All patients (n = 30)
Age (years)	
Mean (range)	18.4 (4.0-40.7)
< 18 years, n (%)	18 (60)
Gender, n (%)	
Male	13 (43.3)
Female	17 (56.7)
PME etiology[a], **n (%)**	
Unverricht-Lundborg disease	7 (23.3)
Mitochondrial disease	7 (23.3)
Neuronal ceroid lipofuscinoses	5 (20.0)
Myoclonus epilepsy and ragged-red fibers	2 (6.7)
Lafora disease	2 (6.7)
Others[b]	6 (20.0)
Concomitant anticonvulsants taken by ≥ 15% of patients, n (%)	
Valproate	23 (76.7)
Clonazepam	12 (40.0)
Lamotrigine	9 (30.0)
Lorazepam	8 (26.7)
Diazepam	5 (16.7)
Baseline seizure counts, n (range)	
Mean for average 10-minute counts	73.5 (0.136-429.7)
Mean for 24-hour counts	9.2 (0.00-58.07)

[a] One patient had an unconfirmed diagnosis of PME.
[b] One PME etiology of metabolic disorder, chromosomal abnormality, Type 3 Gaucher's, Bannayan-Zonana, sialidosis and uncertain.

Results

Thirty patients were enrolled in the study *(table 1)*, of whom 29 (97%) received at least one zonisamide dose and 20 (67%) had evaluable myoclonic seizure counts. One patient did not experience any myoclonic seizures during the study so was excluded from the efficacy analysis (n = 28). Ten patients discontinued the study early: five due to AEs, three for compliance/selection criteria issues, one due to no confirmation of PME, and one for insufficient therapeutic effect. Over the study, zonisamide was administered for a mean of 91 (range 5-132) days and the mean dosage was 172 (range 13-300) mg/day.

Table 2. Reductions in myoclonic seizures with zonisamide in patients with PME[a].

Count type	≥ 50% reduction		≥ 75% reduction (subset of ≥ 50% reduction group)	
	Patients, n (%)	95% CI	Patients, n (%)	95% CI
Average (morning, afternoon, and evening counts), n = 16	6 (38)	15.2, 64.6	4 (25)	7.3, 52.4
Morning, n = 16	6 (38)	15.2, 64.6	4 (25)	7.3, 52.4
Afternoon, n = 16	3 (19)	4.1, 45.6	2 (13)	1.6, 38.3
Evening, n = 16	6 (38)	15.2, 64.6	4 (25)	7.3, 52.4
24-hour counts, n = 12	4 (33)	9.9, 65.1	2 (17)	2.1, 48.4
Converted to 10-minute counts, n = 28	10 (36)	18.6, 55.9	6 (21)	8.3, 41.0

CI: confidence interval.
[a] Intent-to-treat population defined as patients who received at least one dose of zonisamide and experienced at least one myoclonic seizure during study. One patient did not experience any myoclonic seizures during the study so has been excluded from the efficacy analysis.

Safety analysis showed that 90% of patients (n = 27/30) experienced AEs and that the majority (91%, n = 154/169) of these events were mild to moderate in nature. Treatment-related AEs (TRAEs) were reported by 53% of patients (n = 16/30) and the most common were decreased appetite (23%, n = 7/30), somnolence (17%, n = 5/30), asthenia (13%, n = 4/30), and nervousness (10%, n = 3/30). Only two patients withdrew from the study due to TRAEs (asthenia, tremor, anorexia in one patient, and for the second patient please see the commentary below). Six patients experienced serious adverse events (SAEs), including a 9-year-old girl with end-stage Batten disease who died. She experienced sepsis and respiratory failure (not considered related to zonisamide), and abnormal liver function and multisystem organ failure (considered to be zonisamide-related). The remaining SAEs were not considered to be related to zonisamide. Four patients reported increased seizure activity (convulsions), but these resolved during the study.

Efficacy analysis showed that median myoclonic seizure counts, recorded either during 10-minute epochs (n = 16) in the morning, afternoon, and evening and averaged, or over 24-hour periods (n = 12), demonstrated a ≥ 50% myoclonic seizure reduction in 38% (n = 6/16) and 33% (n = 4/12) of patients, respectively *(table 2)*. Four patients were seizure-free during the maintenance phase and six patients had an increase in myoclonic seizure counts from baseline to the maintenance period. Overall, the median reduction in seizure frequency was 55% (converted 10-minute counts). For those counting during 10-minute epochs, the median reduction from baseline was 27% for morning periods, 13% for afternoon periods, 35% for evening periods, and 29% for the average of all periods. The reduction in median seizure frequency was 66% for counts over 24-hour periods.

In an extension of this study (ZNS-505), five patients continued on zonisamide treatment (treatment durations: 759, 181, 84, 734 and 370 days) because they required dosing with capsules smaller than the 100 mg size, (which at the time were not commercially available). Patients who could be treated using only 100 mg capsules were not eligible to enter the extension phase. However, due to the small patient population size, this was primarily a safety study with limited efficacy results. No unexpected AEs were reported during the long-term study, with the majority (88%) of AEs being mild to moderate in nature and only one TRAE (mild tiredness). Of the three patients who reported seizure frequencies at both baseline (maintenance visit) and the final visit, one had a decrease in myoclonic seizures.

Discussion

Due to the complexity of the syndromes associated with PME, treatment of seizures, especially myoclonic seizures, remains a challenge. Many PME syndromes are associated with physical deterioration as the syndrome progresses (Leppik, 2003). Furthermore, clinical study design is impacted by the severity of PME, especially with regards to recording and analyzing seizure frequency. To date, no formal, double-blind, placebo-controlled clinical trials have investigated the treatment of PME. This small, open-label study suggests that zonisamide may have a role to play in the management of PME, demonstrating improved myoclonic seizure control in patients previously refractory to other AEDs. Overall, 36% of patients achieved a 50% reduction in myoclonic seizure frequency and 21% achieved a 75% reduction.

Most patients in this open-label study experienced adverse events, the most common of which were decreased appetite, somnolence, asthenia, and nervousness. These adverse events were generally mild to moderate in severity, a finding consistent with the zonisamide safety database.

A number of patients in this study received concomitant AEDs and there is a possibility of pharmcokinetic interac-

tions, most notably with substances that can induce or inhibit CYP3A4 (an enzyme which is involved in the metabolism of zonisamide) (Eisai Ltd, 2007). Zonisamide is lower in patients with epilepsy receiving CYP3A4-inducing agents such as phenytoin, carbamazapine, and phenobarbitone. These effects are unlikely to be of clinical significance when zonisamide is added to existing therapy, but if CYP3A4-inducing AEDs are withdrawn, dose-adjusted, or introduced, an adjustment of the zonisamide dose may be required. Based upon clinical data, known specific and non-specific CYP3A4 inhibitors appear to have no clinically relevant effect on zonisamide pharmacokinetic exposure parameters.

Zonisamide appears to be effective and generally well tolerated in patients with PME, but as this study was small and open-label in design, caution should be used when interpreting the results. Further research is warranted to investigate the efficacy and safety of zonisamide in this setting. □

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Appendix A.
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